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TITLE: Interdisciplinary Breast Cancer Training Program

PRINCIPAL INVESTIGATOR: Coral A. Lamartinieri, Ph.D.

CONTRACTING ORGANIZATION: The University of Alabama at Birmingham
Birmingham, Alabama 35294-0111

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13. ABSTRACT (Maximum 200 Words) The goal of the University of Alabama at Birmingham Interdisciplinary Breast Cancer Training Program (IBCTP) is to educate and train predoctoral students in a multidisciplinary environment with a focus on breast cancer research. The aims are to 1)recruit predoctoral trainees to the Interdisciplinary Breast Cancer Training program; 2) assure that predoctoral trainees obtain a broad-based breast cancer education and carry out interdisciplinary breast cancer research; 3)administer this program with sufficient oversight to ensure high-quality education and training, efficient completion of degree requirements, and productive research careers. For academic year 2003-2004, we recruited 3 new students, resulting in a total of 9 students in the IBCTP. The previous 6 students are in good academic standing. The IBCTP hosted 9 scientists to present seminars on cancer related research and to talk to the predoctoral trainees. The Breast Cancer Causation and Regulation course and Breast Cancer Journal Club reveived "very good" evaluations. One second year student and mentor submitted and received a Susan Komen predoctoral award for breast cancer research, and two new research grants were awarded to faculty, in part, because of student data used in the preparation of the grant applications. Five abstracts/presentations were made by 3 students at breast cancer related scientific meetings.				
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INTRODUCTION

The goal of the University of Alabama at Birmingham Interdisciplinary Breast Cancer Training Program (IBCTP) is to educate and train predoctoral students in a multidisciplinary environment with a focus on breast cancer research. The aims are to 1) recruit predoctoral trainees to the IBCTP; 2) assure that predoctoral trainees obtain a broad-based breast cancer education and carry out interdisciplinary breast cancer research; 3) administer this program with sufficient oversight to ensure high-quality education and training, efficient completion of degree requirements, and productive research careers. Our training program is designed to prepare and motivate trainees to pursue careers in the fields of breast cancer causation, prevention, diagnosis, therapy and education.

BODY

The executive committee has undergone two transitions. With the departure of Dr. Fran Kern, Dr. Danny Welch has taken over Mechanisms of Growth Control section and Dr. Therese Strong has taken over Gene Therapy in place of Dr. David Curiel. This remaining members of the executive committee remain: Robert B. Diasio (Cancer Pharmacology), Clinton Grubbs (Chemoprevention), Charles N. Falany (Cancer Causation), and Dr. Coral A. Lamartiniere (Program Director), plus one elected student/trainee, Craig Rowell. The executive committee is responsible for interviewing and selecting prospective IBCTP students, developing and implementing the academic and research program, review of individual student progress, the budget, and participating in Quarterly and Annual Program reviews.

TASKS FOR YEAR THREE (9/02 - 8/03)

1) Schedule IBCTP seminar speakers (Aim 2).

The APPENDIX contains the list of breast cancer seminar speakers.

2) Hold quarterly program reviews (Aim 3).

Quarterly program reviews were held by the executive committee to discuss, recruitment, the progress of the trainees, the curriculum and the evaluation of courses.

3) Monitor progress of trainees (Aim 3).

At the quarterly meetings, progress of individual students was discussed. At the end of the summer meeting, laboratory evaluations turned in by the mentors were taken into consideration. To date, all students are making satisfactory progress academically and in research.

4) Evaluate Breast Cancer Journal Club course (Aim 3)

Breast Cancer Journal Club was discussed and a slightly new format was implemented for year 4. While the presenter and all attendees are expected to participate, 4 primary discussants are assigned to enhance the overall interactions. To date, this is working very well.

5) Attend AACR meeting.

The Program Director (Lamartiniere) and 2 Breast Cancer students (Rowell and Whitsett) attended and made platform and poster presentations. A list of the abstracts/presentations is contained in the APPENDIX. Students attended other meetings, including the Era of Hope DOD Breast Cancer Research Program Meeting in Orlando (See Abstracts/Presentations) where breast

cancer was a focus.

6. Hold annual program review (Aim 3).

At the end of the summer executive committee meeting, the following recommendations were made.

While the Breast Cancer Causation and Regulation course received a very good evaluation, it was recommended that the Mathematical Model of Cancer lecture be deleted since all students are now taking a full course in biostatistics. The Estrogens and Breast Cancer lecture was also discontinued with some of the contents moved to Steroid Hormone Action in the Breast lecture. With the addition of 2 new faculty, 2 new lectures were added for year 4: Tumor-Host/Stroma Interactions (Dr. Rosa Serra) and Cancer Regulation (Dr. Danny Welch). A copy of course content is enclosed in the APPENDIX. Also, Dr. Serra's and Welch's Biographical Sketches are enclosed.

It was also recommended that we request a no cost continuation of one year (for 1/9/04-30/8/05) with potential funds that can be made available by moving some of the present second and third year students to some of the mentors' research grants, and graduate school and departmental funds. Having students paid off of research grants, starting in their second year, is a normal procedure at UAB and this would allow unused DOD money to be spent on recruiting and supporting more new Breast Cancer students in 2004-2005. Since DOD is not providing the opportunity for predoctoral training grant to be renewed, we intend to submit an R25 application to NIH to continue this specific training. In the mean time, this continuation would bridge us to 2005. We have been successful in recruiting very good students and we have the faculty to mentor the students. Faculty in the Integrative Biomedical Sciences give high praise to our students.

7) Prepare and submit annual report to DOD.
Submitted.

KEY ACCOMPLISHMENTS

- Retained 6 predoctoral Breast Cancer students. The second year students, Hope Amm and Tim Whitsett have selected their mentors (Drs. Don Buchsbaum and Coral Lamartiniere, respectively).
- Recruited 3 more predoctoral Breast Cancer students. Their credentials are provided in the APPENDIX.
- For academic year 2002-2003, 6 applicants (from 39 completed applications) were interviewed and fellowships were offered to and accepted by 3 students (James Cody, April Adams, Kevin Roarty).
- The appendix contains the lectures for the Breast Cancer Causation and Regulation course for 2002. Changes in this course take into consideration the course evaluation by the students and course director. The course in 2002 received a "very good" evaluation.
- Submitted and received Susan Komen Breast Cancer Predoctoral Award for one student

and received 2 breast cancer research grants based in part on preliminary data from trainee.

REPORTABLE OUTCOMES

1) We have 9 students enrolled *via* the IBCTP.

2) Abstracts/Presentations

Bowe, D.B., Jones, M., Page, G.P., Allison, D.B., and Frost, A.R.: "Differences in gene expression of breast carcinomas of pre- and post-menopausal women." Era of Hope DOD Breast Cancer Research Program Meeting, Orlando, FL, Sept. 25-28, 2002.

Rowell, C., Isbell, S., Desilva, T and Lamartiniere, C.A. 2-Dimensional gel electrophoresis and proteomic identification of mammary gland proteins of rats treated with the soy isoflavone, genistein. Proceedings of the American Association for Cancer Research. 43:35, 2002.

Rowell, C., Whitsett, T., Carpenter, M. and Lamartiniere, C.A. Proteomic Analysis of Uterine Proteins Following Genistein Exposure. Proceedings of the American Association for Cancer Research. 44: 713, 2003.

Bowe, D.B., Jones, M., Sadlonova, A., Page, G.P., Allison, D.B., and Frost, A.R.: "Age-related gene expression profiles for invasive breast carcinomas in pre- and post-menopausal women." Mammary Gland Biology, Gordon Research Conference, Bristol, RI, June 1-6, 2003.

Whitsett, T. and Lamartiniere, C.A. Genistein regulates GRIP-1 in the rat mammary and uterus. Presented at South Central Society of Toxicology Meeting in Chattanooga TN, September, 2003.

3) Predoctoral Award

Susan Komen Breast Cancer Predoctoral Award (DISS0201242)

P.I.: Dr. C.A. Lamartiniere; Predoctoral Student: Craig Rowell

First year: \$30,000; Total: \$60,000; 5/1/03 – 4/30/05

Grant Title: Effects of Genistein and TCDD on the Maturation of the Rat Mammary Gland: Alterations in Protein Tyrosine Kinase Activity and Signaling.

4) Research grants received in part because of preliminary data produced by Breast Cancer predoctoral student, Craig Rowell

NIEHS 1R21 ES012326-01 (C.A. Lamartiniere, PI)

4/18/03 – 3/30/06

First Year: \$100,000; Total: \$300,000

In Utero TCDD Programming for Mammary Cancer: Proteomic analysis of mammary gland from rats treated in utero with TCDD.

DOD DAMD BC 17-03-1-0433 (C.A. Lamartiniere, PI)

7/1/03-7/31/06

First Year: \$150,000; Total: \$428,249

Proteomic Analysis of Genistein Mammary Cancer Chemoprevention: Proteomic analysis and interstitial fluid analysis of mammary glands of rats treated with genistein.

APPENDIX

Student Credentials

IBCTP Seminar Speakers

2003 Breast Cancer Caustion and Regulation Lectures

Biographical Sketches for Drs. Rosa Serra and Danny Welch

Students Enrolled in the University of Alabama at Birmingham Interdisciplinary Breast Cancer Training Program

<u>Student</u>	<u>Previous Degree Institution</u>	<u>Date of Entry</u>	<u>GPA</u>	<u>GRE</u>	
				<u>Verbal</u>	<u>Quantitative Analytical</u>
Craig Rowell	BS (95) Lake Forest IL MS (00) UAB	2000	3.8	580	610 680
Chantelle Bennetto	BS (99) U. Saskatoon Canada	2000	4.0	510	660 710
Mubina Nasrin	MD (94) M.R. Medical College, India	2001	no GPA	690	650 670
Damon Bowe	BS (99) Bates College Maine	2001	3.5	590	580 710
Hope Amm	BS (02) Saint Mary's College	2002	3.38	550	640 490
Timothy Whitsett	BS (02) Yale University	2002	3.59	530	700 750
James Cody	BS (01) UAB	2003	3.37	590	670 640
April Adams	BS (01) U. Chicago	2003	3.38	660	710 -
Kevin Roarty	BS (95) Virg. Tech. M.S. (02) UAB	2003	3.74	520	680 480

**2002-2003 University of Alabama at Birmingham
Interdisciplinary Breast Cancer Training Program Seminars**

- | | |
|-------------------|---|
| October 1, 2002 | James Shull, Ph.D.
Professor, Eppley Inst. For Research in Cancer & Allied Diseases
University of Nebraska Medical Center
"Genetic Determinants of Susceptibility to Estrogen-Induced Mammary Carcinogenesis in the ACI Rat" |
| October 22, 2002 | Lakshmi Pendyala, Ph.D.
Director, Pharmacokinetics/Pharmacodynamics
Department of Medicine
Roswell Park Cancer Inst., Buffalo, NY
"Oxaliplatin: In Vitro and Translational Studies" |
| November 19, 2002 | Xinbin Chen, Ph.D.
Associate Professor
Department of Cell Biology
UAB
"The Transcriptional Activity of p 53 Tumor Suppressor" |
| December 10, 2002 | Jeffrey Rosen, Ph.D.
Professor of Cellular and Molecular Biology
Baylor College of Medicine, Houston
"Regulation of Mammary Epithelial Cell Fate in Normal Development and Breast Cancer" |
| March 4, 2003 | Myles Brown, M.D.
Associate Professor of Medicine
Dana-Farber Cancer Institute
Harvard Medical School
"Coregulators and Cancer" |
| March 4, 2003 | Francis Ali-Osman, Ph.D.
MD Anderson Cancer Center
University of Texas
"Transcriptional and Post-translational Regulation of GSTP1 Signaling and Metabolic Function by Ser/Thr Kinases" |
| April 16, 2003 | Carlos Arteaga, MD
Professor of Medicine and Cancer Biology
Vanderbilt University School of Medicine
"Synergy between the TGF-beta and erbB Signaling Networks in Mammary Neoplasia" |

April 29, 2003

Rosa Serra, Ph.D.
Assistant Professor
UAB Department of Cell Biology
"TGF-B in Stromal-epithelial Interactions in the Mammary Gland"

August 26, 2003

Satyabrata Nandi, Ph.D.
Professor
Dept of Molecular & Cellular Biology
University of California, Berkeley
"Estrogen Can Prevent Breast Cancer"

Breast Cancer Causation and Regulation**TOX 750****Fall 2003****Mondays and Wednesdays, 3-5 pm in Volker Hall 108D**

Course Director: Coral A. Lamartiniere

Volker Hall 124; 4-7139; Coral.Lamartiniere@ccc.uab.edu

Administrative Coordinator: Becky Warnix Volker Hall 101C; 4-4579; Becky.Warnix@ccc.uab.edu

Date	Topic	Instructor (Department)
Wed Sept 3	Overview of the Breast Cancer Problem	John Waterbor (Epi)
Mon Sept 8	Environmental Carcinogenesis	Coral Lamartiniere (Pharm/Tox)
Wed Sept 10	Steroid Hormone Action in the Breast	Barnes (Pharm/Tox)
Mon Sept 15	Oncogenes and Suppressor Genes	Mike Ruppert (Medicine)
Wed Sept 17	Signal Transduction and Breast Cancer	Jeffrey Kudlow (Endocrinology)
Mon Sept 22	Exam	
Wed Sept 24	Nuclear Receptors as Targets for Novel Small Molecule Therapeutics	Donald Muccio (Chemistry)
Mon Sept 29	Tumor-host/stroma Interactions	Rossa Serra (Cell Biol)
Wed Oct 1	Primary Prevention	Mona Fouad (Preventive Medicine)
Mon Oct 6	Chemically-induced Models of Breast Cancer (Chemoprevention)	Clinton Grubbs (Chemoprevention)
Wed Oct 8	Cancer Pharmacology	Robert Diasio (Pharm/Tox)
Mon Oct 13	Exam	
Wed Oct 15	Pathology of Breast Cancer	Andra Frost (Pathology)
Mon Oct 20	Targeted Immunotherapy	Denise Shaw (Medicine)
Wed Oct 22	Breast Cancer Metastasis	Joanne Douglas (Pathology)
Mon Oct 27	Gene Therapy	Theresa Strong (Gene Therapy)
Wed Oct 29	Cancer Regulation	Danny Welch (Pathology)
Mon Nov 3	Exam	

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME		POSITION TITLE	
Rosa Serra		Assistant Professor	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
St. Louis University, St. Louis, Missouri	B.S.	1986	Biology
The Pennsylvania State University, College of Medicine, Hershey, PA	Ph.D.	1992	Cell and Molecular Biology
Vanderbilt University School of Medicine, Nashville, TN	Post-doctoral	1992-1995	Cell and Developmental Biology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

A. Positions and Honors.**Employment**

1995 to 1999	Department of Cell Biology, Vanderbilt University School of Medicine, Nashville, Research Assistant Professor
1999-2002	Department of Molecular and Cellular Physiology, University of Cincinnati. Assistant Professor
2000-2002	Member of Developmental Biology Graduate Program Children's Hospital Research Institute, Cincinnati
2002-present	Department of Cell Biology, the University of Alabama at Birmingham Assistant Professor
2002-present	Graduate Faculty member, Department of Cell Biology and the Cellular and Molecular Biology Graduate Program, the University of Alabama at Birmingham. Associate Scientist Center for Metabolic Bone Disease, Arthritis and Musculoskeletal Center, Cancer Center, and Center for Adhesion and Matrix Research, UAB.

Additional Training

June 1993	American Association for Cancer Research Histopathobiology of Neoplasia Workshop, Keystone, CO
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Number pages consecutively at the bottom throughout the application. Do not use suffixes such 3a, 3b.

FF

Principal Investigator/Program Director (Last, first, middle):

Scientific Service

Scientific program committee ASBMR for 2001 meeting.
Ad hoc member PTHC study section NIH, February 2002.
Ad hoc Comparative Medicine special review panel, March 2002.
Scientific program committee ASBMR for 2002 meeting.
Ad hoc member CAMP study section, NIH October, 2002
Scientific program committee ASBMR for 2003 meeting.
Ad hoc member ORTH study section NIH February 2003
Scientific Program Committee ASBMR, 2003 meeting
Mail in review, CAMP study section, June 2003
Ad hoc member OBM2 study section, NIH, Oct 2003

B. Peer Reviewed Publications

Hu J, Camper S, Tilghman S, Miller T, Georgoff I, **Serra R**, and Isom HC: Characterization of SV40-immortalized hepatocyte cell lines: functional analyses of albumin gene transcription. *Cell Growth and Differentiation*, 3:577-588, 1992.

Serra R, Verderame MF, and Isom HC: TGF β 1 suppresses the transformed phenotype in *ras*-transformed hepatocytes. *Cell Growth and Differentiation* 3:693-704, 1992.

Serra R and Isom HC: Stimulation of DNA synthesis and proto-oncogene expression in hepatocytes in DMSO culture. *J. of Cellular Physiology* 154:543-553, 1993.

Serra R, Carbonetto S, Lord M, and Isom HC: TGF β 1 suppresses transformation in hepatocytes by regulating α 1 β 1 integrin expression. *Cell Growth and Differentiation*, 5:509-517, 1994.

Serra R, Pelton RW, and Moses HL: TGF β 1 inhibits branching morphogenesis and *N-myc* expression in lung bud organ cultures. *Development*, 120:2153-2161, 1994.

Serra R and Moses HL: pRb is necessary for inhibition of *N-myc* expression by TGF β 1 in embryonic lung organ cultures. *Development*, 121(9):3057-3066, 1995.

Serra R, Johnson M, Filvaroff E, Laborde J, Sheehan D, Derynck R, Moses HL: Expression of a truncated kinase defective TGF- β type II receptor in mouse skeletal tissue results in defects in chondrocyte differentiation and an osteoarthritis-like phenotype. *Journal of Cell Biology* 139:541-552, 1997.

Gorska AE, Joseph H, Derynck R, Moses HL, **Serra R**: Dominant-negative interference of the TGF- β type II receptor in mammary epithelium results in alveolar hyperplasia and differentiation in virgin mice. *Cell Growth and Differentiation* 9:229-238, 1998.

Joseph H, Gorska AE, Sohn P, Moses HL, **Serra R**: Transgenic mice that express a truncated kinase defective TGF- β type II receptor in the mammary gland stroma demonstrate increased lateral duct branching. *Molecular Biology of the Cell* 10:1221-1234, 1999.

Serra R, Karapalis A, Sohn P: PTHrP-dependent and -independent effects of TGF- β 1 on endochondral bone formation. *Journal of Cell Biology* 145:783-794, 1999.

McDonnell M, Law B, **Serra R**, Moses HL: Antagonistic Effects of TGF β 1 and BMP-6 on Skin Keratinocyte Differentiation. *Exp Cell Res.* 263(2):265-273, 2001.

Alvarez J, Horton J, Sohn P, **Serra R**: The perichondrium plays an important role in mediating the effects of TGF- β 1 on endochondral bone formation. *Developmental Dynamics* 221:311-321, 2001.

Bragg A, Moses HL, **Serra R**: Signaling to the Epithelium is Not Sufficient to Mediate all of the Effects of TGF- β 1 and Bmp4 on Murine Embryonic Lung Branching Morphogenesis, Mechanisms of Development 109:13-26, 2001.

Alvarez J, Sohn P, Zeng X, Doetchman T, Robbins D, **Serra R**: TGF- β 2 mediates the effects of Hedgehog on Hypertrophic Differentiation and PTHrP Expression. Development 129:1913-1924, 2002.

Sohn P, Crowley M, Slattery E, **Serra R**: Developmental and TGF- β -mediated regulation of ANK mRNA expression in cartilage. Osteoarthritis and Cartilage 10:482-490, 2002.

Submitted:

Wang G, Woods A, Sabari S, Khan S, Pagnotta L, **Serra R**, Stanton L-A, Beir F: RhoA/ROCK signaling suppresses hypertrophic chondrocyte differentiation. Submitted, 2003

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Number pages consecutively at the bottom throughout the application. Do not use suffixes such 3a, 3b.

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Principal Investigator/Program Director (Last, first, middle):

Alvarez J, Costales L, **Serra R**, Balbin M, Lopez JM: Matrix metalloproteinases and vascular endothelium growth factor are expressed according to a precise spatiotemporal pattern during development of the secondary ossification center of the rat tibia. Submitted, 2003

Bailey J, Neiport K, Herbst M, Srivasta S, **Serra R**, Horseman N: Prolactin and Transforming growth factor-beta signaling exert opposite effects on mammary gland morphogenesis, involution, and signaling via the Akt-forkhead pathway. Submitted 2003

Reviews and Commentaries

Moses HL, Arteaga CL, Alexandrow MG, Dagnino L, Kawabata M, Pierce DF, and **Serra R**: TGF β regulation of cell proliferation. Princess Takamatsu Symposium. 24: 250-263, 1994.

Serra R and Moses HL: Tumor Suppressor Genes in the TGF- β Signaling Pathway? Nature Medicine 2(4):390-391, 1996.

Moses HL and **Serra R**: Regulation of Differentiation by TGF- β . Current Opinion in Genetics and Development, 6: 581-586 October, 1996.

Serra R, McDonnell M, and Bragg A: El factor de Crecimiento Transformante beta en el Desarrollo y Enfermedad. Biotechnologia Aplicada, 16:205-218, 1999.

Serra R: Transforming Growth Factor beta (TGF beta). Encyclopedia of Life Sciences, MacMillan Reference Limited, Stockton Press.

Serra R and Crowley M: TGF- β s in mammary gland development and breast cancer. Breast Disease, In Press, 2003.

Serra R: TGF- β signaling in human skeletal and patterning disorders, Embryo Today, In press, 2003.

C. Research Projects Completed and Ongoing for the Past Three Years

R01 AR45605 Serra (PI) 4/1/2003 through 3/31/2008

"TGF- β SIGNALING IN CHONDROCYTE DIFFERENTIATION"

The major goal of this project is to determine the mechanism of TGF- β action in endochondral bone formation.

Role: PI

R01 AR46982 Serra (PI) 5/1/00 through 4/30/05

"MECHANISM OF CHONDROPROTECTION BY TGF- β "

The major goal of this project is to determine how TGF- β regulates formation and persistence of articular cartilage.

Role: PI

R01 CA91974 Serra (PI) 7/1/2001 through 6/30/2006

"TGFB IN STROMAL-EPITHELIAL INTERACTIONS IN MAMMARY GLAND"

The major goal of this project is to determine the role of TGF- β signaling to the stroma in regulation of branching morphogenesis and tumor formation in mouse mammary gland.

Role: PI

The Department of the Army Office of Congressionally Directed Research, Post-doctoral Fellowship

Crowley (PI) 8/1/01 through 7/31/04

"THE INFLUENCE OF STROMAL TGF- β RECEPTOR SIGNALING ON MOUSE MAMMARY NEOPLASIA"

Role: Mentor

Charlotte Geyer Foundation Horseman (PI) 12/1/00 through 5/31/01

"Stages of Breast Development: Normal to Metastatic Disease"

Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME		POSITION TITLE	
Danny R. Welch		Leonard H. Robinson Professor of Pathology	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of California - Irvine	B.S.	1980	Biology (Cell Biology)
University of Texas -Houston (M.D. Anderson Cancer Ctr.)	Ph.D.	1984	Biomedical Sciences (Tumor Biology)
M.D. Anderson Cancer Center (Advisor: G.L. Nicolson)	Postdoc	1984	Metastasis

NOTE: The Biographical Sketch may not exceed four pages. Items A and B may not exceed two of the four-page limit.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

The Upjohn Company

8/84-6/88 Scientist I: Department of Cancer and Infectious Diseases Research
7/88-10/88 Scientist II: Department of Cancer and Infectious Diseases Research

Glaxo, Inc.

10/88-10/89 Senior Scientist III: Department of Chemotherapy,
10/89-5/90 Research Investigator: Department of Chemotherapy

The Pennsylvania State University College of Medicine

11/02-06/03 Adjunct Associate Professor of Pathology
07/97-10/02 Associate Professor of Pathology (tenured 1999), Jake Gittlen Cancer Research Institute
02/02-10/02 Associate Professor of Pharmacology
10/01-09/02 Director, Penn State-Natl. Fndn. Cancer Res. Center for Metastasis Research
11/90-6/97 Assistant Professor, Jake Gittlen Cancer Research Institute, Department of Pathology
11/91-present Member - Graduate Faculty, The Pennsylvania State University

The University of Alabama at Birmingham

11/02-present Leonard H. Professor of Pathology, Division of Molecular and Cellular Pathology
11/02-present Senior Member, Comprehensive Cancer Center
11/02-present Member, Graduate Faculty
10/02-present Director, National Foundation for Cancer Research Center for Metastasis Research

Study Sections and Other Professional Activities

Member - Carcinogenesis, Nutrition & Environment Committee—American Cancer Society (1997-2003; Vice-chair 2002; Chair 2003)
Member - U.S. Army Research and Materiel Command—Breast & Prostate Cancer Panels (1995-2003)
Chair, California Cancer Research Program — Biomedical Study Section C (2000, 2002)
Member - California Breast Cancer Research Program — Basic Breast Biology (2000, 2001)
Member, *Ad hoc* - U.S. Public Health Service - NCI (P30, U01, P01, RO1 grants) (1998-2004)
Member - NASA Biomedical review panel (1997, 1999)
Ad hoc, New Jersey Cancer Control Comm, Susan Komen Fndn, Am. Inst. Cancer Res., Breast Cancer Soc. Canada, Netherlands Cancer Inst., Italian Cancer Inst., World Fndn. Cancer Res.
Medical Director-at-Large, American Cancer Society - Pennsylvania Division (1992-2001)

Editorial Boards: *Anti-cancer Drugs*, *Cancer Research*, *Cancer & Metastasis Reviews*, *Clinical and Experimental Metastasis*, *Journal of Mammary Gland Biology and Neoplasia*, *Molecular Cancer Therapeutics*

Awards/Honors: American Cancer Society PA-Division Chairman's Award for Outstanding Efforts in Cancer Control (2000)

B. Selected peer-reviewed publications. Total — 97 Peer-reviewed; 137 abstracts; 17 book chapters; Editor 3 books):

Welch, D.R., (5 others) & Weissman, B.E. Microcell-mediated transfer of chromosome 6 into metastatic human C8161 melanoma cells suppresses metastasis, but not inhibit tumorigenicity. *Oncogene* (1994) 9: 255-262.
Phillips, K., Welch, D.R., (3 others) & Weissman, B. (1996) Suppression of MDA-MB-435 breast carcinoma cell metastasis following the introduction of human chromosome 11. *Cancer Res* 56: 1222-1227.
Lee, J.-H., (5 others) and Welch, D.R. (1996) KiSS-1, A novel malignant melanoma metastasis-suppressor genes identified in chromosome 6-malignant melanoma microcell hybrids. *J Natl Cancer Inst* 88: 1731-1737.
Welch, D.R. (1997) Technical considerations when studying metastasis in vivo. *Clin Exptl Metastasis* 15:272-306.
Welch, D.R. and Wei, L.L. (1998) Molecular genetics of breast cancer metastasis. *Endocrine-related cancers* 5: 155-96.
Welch, D.R. and Rinker-Schaeffer, C.W. (1999) What defines a useful marker of metastasis in human cancer? *J Natl Cancer Inst* 91: 1351-1353.

- Kiley, S.C., Clark, K.J., Goodnough, M., **Welch, D.R.** and Jaken, S. (1999) Dominant-negative protein kinase C- δ inhibits the metastatic progression of mammary tumor cells in syngeneic rats. *Oncogene* 18: 6748-6757.
- Miele, M.E., (9 others) and **Welch, D.R.** (2000) Human melanoma metastasis-suppressor locus maps to 6q16.3-q23. *Int J Cancer* 86: 524-528.
- Goldberg, S.F., Harms, J.F., Quon, K. and **Welch, D.R.** (2000) Metastasis-suppressed C8161 melanoma cells arrest in lung but fail to proliferate. *Clin Exptl Metastasis* 17: 601-607
- Welch, D.R.**, (10 authors), Alessandrini, A. (2000) Transfection of constitutively active Mek1 confers tumorigenic and metastatic potentials to NIH3T3 cells. *Cancer Res* 60: 1552-1556.
- Seraj, M.J.*, Samant, R.S.*, Verderame, M.F., **Welch, D.R.** (2000) Functional evidence for a novel human breast carcinoma metastasis suppressor, BRMS1, encoded at chromosome 11q13 *Cancer Res* 60: 2764-2769.
- Yoshida, B., **Welch, D.R.** Rinker-Schaeffer, C.W. (2001) Metastasis suppressor genes: a review and perspective on an emerging field. *J Natl Cancer Inst* 92: 1717-1730.
- Rinker-Schaeffer, C.W., **Welch, D.R.**, Sokoloff, M. (2001) Defining the biological role of genes that regulate prostate cancer metastasis. *Curr Opin Urology* 10: 397-401.
- Saunders, M.M., (4 others), **Welch, D.R.**, Donahue, H.J. (2001) Breast cancer metastatic potential correlates with a breakdown in homospesific and heterospesific gap junctional intercellular communication. *Cancer Res* 61: 1765-1767.
- Rieber, M., **Welch, D.R.**, Strasberg-Rieber, M. (2001) Suppression of C8161 melanoma metastatic ability by chromosome 6 induces differentiation-associated tyrosinase and decreases proliferation on adhesion-restrictive substrates through overexpression of p21^{WAF1} and down-regulation of bcl-2 and cyclin D3. *Biochem Biophys Res Comm* 281: 159-165.
- Pethiyagoda, C.L., **Welch, D.R.**, Fleming, T.P. (2001) Dipeptidyl peptidase IV (DPPIV) inhibits cellular invasion of melanoma cells. *Clin Exptl Metastasis* 18: 391-400.
- Seraj, M.J., Harding, M.A., Gildea, J.J., **Welch, D.R.**, and Theodorescu, D. (2001) The relationship of BRMS1 and Rho-GDI2 to gene expression to metastatic potential in lineage-related human bladder cancer cell lines. *Clin Exptl Metastasis* 18:519-525.
- Samant, R.S.(13 others), & **Welch, D.R.** (2001) Analysis of mechanisms underlying BRMS1 suppression of metastasis. *Clin Exptl Metastasis* 18:683-693.
- Lukes, L., (4 others), **Welch, D.R.**, Hunter, K.W. (2001) Hereditary predisposition to efficient metastatic progression is linked to the breast cancer metastasis suppressor gene BRMS1. *Cancer Research* 61:8866-8872.
- Debies, M.T. & **Welch, D.R.** Genetic basis of human breast cancer metastasis. (2001) *J Mamm Gland Biol Neoplasia*. 6: 441-451.
- Samant, R.S., (3 others), & **Welch, D.R.** (2002) Genomic structure of the human breast carcinoma metastasis suppressor gene, BRMS1. *Intl J Cancer* 97:15-20.
- Manni, A., (6 others) & **Welch, D.R.**, (2002) Polyamine involvement in invasion and metastasis by human breast cancer cells. *Clin Exptl Metastasis* (In press).
- Shevde, L.A., (6 others) & **Welch, D.R.**, (2002) Suppression of human melanoma metastasis by the metastasis suppressor gene, BRMS1. *Experimental Cell Research* 273: 229-239.
- Samant, R.S., (2 others) & **Welch, D.R.** (2002) Cloning and partial characterization of *Brms1*, the murine homolog of the human breast carcinoma metastasis suppressor gene, *BRMS1*. *Clin Exptl Metastasis* 18: 683-693.
- Manni, A., (6 others) and **Welch, D.R.**, (2002) Polyamine involvement in invasion and metastasis by human breast cancer cells. *Clinical and Experimental Metastasis* 19:95-105.
- Park, Y.G., Lukes, L., Yang, H., Debies, M.T., Samant, R.S., **Welch, D.R.**, Lee, M., Hunter, K.W. Comparative sequence analysis in eight inbred strains of the metastasis modifier QTL candidate gene *Brms1*. *Mammalian Genome* 13: 289-292.
- Mastro, A.M., Gay, C.V. and **Welch, D.R.** (2003) The skeleton as a unique environment for breast cancer cells. *Clinical and Experimental Metastasis* 19: 3: 275-284
- Meehan, W.J. and **Welch, D.R.** (2003) Breast cancer metastasis suppressor 1: Update. *Clin. Exptl Metastasis* 20(1): 45-50.
- Welch, D.R.**, Harms, J.F., Mastro, A.M., Gay, C.V., Donahue, H.J. (2003) Breast cancer metastasis to bone: Research challenges and opportunities. *Journal of Musculoskeletal and Neuronal Interactions*. 3: 30-38.
- Goldberg, S.F., Miele, M.E., Hatta, N., Takata, M., Paquette-Straub, C., Freedman, L.P. and **Welch, D.R.** Melanoma metastasis suppression by chromosome 6: Evidence for a pathway regulated by DRIP130/CRSP3 and VDUP1. *Cancer Research* 63:432-440.
- Harms J.F., Budgeon L.R., Christensen N.D., **Welch D.R.** Maintaining GFP tissue fluorescence through bone decalcification and long-term storage. *Biotechniques* 2002; 33(6): 1197-1200.
- Welch, D.R.**, Harms, J.F., Mastro, A.M., Gay, C.V., Donahue, H.J. (2003) Breast cancer metastasis to bone: Research challenges and opportunities. *Journal of Musculoskeletal and Neuronal Interactions*. 3: 30-38.
- Harms, J.F. and **Welch, D.R.** (2003) MDA-MB-435 human breast carcinoma metastasis to bone. *Clinical and Experimental Metastasis* 19: 327-334.
- Manni,A., Washington, S., Craig, L., Cloud, M., Griffith, J.W., Verderame, M.F., Texter, L.J., Mauger, D., Demers, L.M., Harms, J.F., and **Welch, D.R.** *Clinical and Experimental Metastasis* 19: 321-325.
- Hunter, K.W., **Welch, D.R.** and Liu, E.T. (2003) Genetic Background is a Major Determinant of Metastatic Potential. *Nature Genetics* 34: 23-24.
- Shevde-Samant, L.A. and **Welch, D.R.** (2003) Metastasis suppressor pathways – an evolving paradigm. *Cancer Letters* 198: 1-20.
- Welch, D.R.** and Hunter, K.W. (Invited Editorial) Another metastasis suppressor identified in prostate cancer. *Journal of the National Cancer Institute* 95:839-841.
- Mastro, A.M., Gay, C.V., Donahue, H.J., Jewell, J., DiGirolamo, D., Chislock, E.M., Guttridge, K., and **Welch, D.R.** Breast cancer cells induce osteoblast apoptosis: a possible contributor to bone degradation. *J. Cell. Biochem.* (In press).
- Meehan, W.J., Samant, R.S., Hopper, J.E., Carozza, M.J., Shevde, L.S., Workman, J.L., Eckert, K.E., Michael F. Verderame, & **Welch, D.R.** Interaction of the BRMS1 metastasis suppressor with RBP1 and the mSin3 histone deacetylase complex. *J. Biol. Chem* (In press).

- C. Research Support. List elected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and responsibilities of principal investigator identified above.

ACTIVE

5R01 CA87728-02 (Welch) PHS/NCI Molecular Regulation of Breast Cancer Metastasis Goals: Biochemical characterization of BRMS1, a human breast cancer metastasis suppressor gene.	07/01/00 - 06/30/04 \$202,500	35%
BC010286 (Welch) Department of Defense - Idea Metastasis Genes in Breast Cancer to Bone Goals: To determine whether chromosome 11 and osteopontin are determinants of breast cancer metastasis to bone.	05/31/02 - 06/30/05 \$97,363 D.C.	10%
No Identifying Number (Welch) National Foundation for Cancer Research NFCR Center for Metastasis Research Goals: I am the director of a multi-investigator, multi-institutional team studying metastasis. The center provides funding for seed grants among members. Initial studies will focus on bone metastasis and melanoma metastasis.	10/01/01 - 9/30/03 \$125,000 D.C.	5% (no salary)
DAMD17-01-1-0362 (Welch, PI, Postdoctoral Fellowship) U.S. Army Medical Research & Materiel Command Understanding the Mechanism of Action of Breast Metastasis Suppressor BRMS1 Goal: Postdoctoral Fellowship [Rajeev S. Samant]	07/01/01 - 06/30/04 \$50,000	minimal
HSF-GEF Scholar's Fund University of Alabama at Birmingham Goal: Equipment grant to purchase of animal caging systems.	01/01/03 - 12/31/03 \$100,000	minimal
R50 CA89019 (Bland) PHS/NCI SPOR in Breast Cancer. Project #2 (Project Director): Molecular Regulation of Breast Cancer Metastasis Goals: (1) Test whether metastasis suppressor gene expression correlates with frequency and distribution of breast cancer metastasis in patients. (2) To develop osteotropic breast cancer cell lines and test whether BRMS1 is a metastasis suppressor gene to bone.	10/01/03 - 09/30/05 \$211,242	25%

COMPLETED (amounts listed are total direct costs)

Genzyme Corporation (Welch) Compound Screening	10/05/98 - 10/16/01 \$54,042	minimal
Pharmacia (Welch) Proprietary Study	12/01/00 - 11/30/01 \$74,187	5%
RO1 CA62168 (Welch) PHS/NIH Metastasis Suppressor Gene in Human Cutaneous Melanoma	07/15/94 - 06/31/01 \$961,773	35%
DAMD17-96-1-6152 (Welch) U.S. Army Medical Research & Materiel Command Molecular Mechanisms of Metastasis Suppression Human Breast Cancer	07/01/96 - 06/30/00 \$785,901	25%
RO1 CA66021 (Fountain - Welch Subcontract) PHS/NCI Dissecting the roles of chromosome 11q genes in human melanoma	08/01/97 - 07/31/99 \$24,626	10%
D1550100403 (Welch) Susan G. Komen Breast Cancer Foundation Study of BRMS 1 Mechanisms of Action Using a Hemozygous Null Knock-out Mouse Goal: Dissertation Research Award	10/01/01 - 04/30/02 \$15,000	minimal
No Identifying number (Welch) Tobacco Settlement Formula Fund Breast Cancer Metastasis to Bone Goals: To obtain pulmonary data necessary for application of program projects grant (Co-investigators: H.J. Donahue, C.V. Gay, A.M. Mastro)	07/01/02 - 06/30/04 \$242,846 D.C.	5% (no salary)
BC010669 (Welch, PI, Pre-doctoral Fellowship) Department of Defense - Postdoctoral fellowship Study of Brms1 Mechanism of Action Using a Homozygous Null Knock-out Mouse Goal: Dissertation Research Award [Michael T. Debies, decided not to move to UAB; so grant was transferred to new PI]	06/01/02 - 05/31/05 \$22,000	minimal
No Identifying Number (Welch) National Foundation for Cancer Research Molecular Basis of Cancer Metastasis Goals: To utilize microarrays for identifying metastasis-associated genes in breast cancer and melanoma. (Now NFCR Center)	10/01/95 - 9/30/03 \$86,956 D.C.	5% (no salary)
1RO1 CA90991-01 (H.J. Donahue) PHS/NCI Intercellular Communication in Breast Cancer Metastasis to Bone Goals: To assess the role of tumor cell-bone cell gap junctions in the development of bone metastasis. This grant may again be listed under active if the universities negotiate how to handle indirect costs.	04/01/01 - 03/31/06 \$166,000 D.C.	10%
BC991163 (Eckert) U.S. Army Med. Res. & Materiel Command Neoplastic Consequences of a Mutator Phenotype in Human Breast Epithelial Cells Goals: To test the hypothesis that a mutator phenotype may be responsible for tumorigenicity and/or progression of human breast cancer. D.R. Welch, Co-investigator, is responsible for all in vivo studies.	07/01/00 - 06/30/03 \$75,306	5%
PDF-2000-218 (Welch, PI, Postdoctoral Fellowship) Susan G. Komen Breast Cancer Foundation BRMS1 as a Prognostic Tool in Breast Cancer Goals: Postdoctoral fellowship to determine if BRMS1 mutations exist in patient specimens and if BRMS1 can be used as a diagnostic/prognostic tool in immunohistochemical studies. [Lalita R. Shevde]	10/01/00 - 9/30/03 \$35,000 D.C.	minimal